



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,291	04/29/2005	Klaus Olaf Bornsen	ON/4-32325A	1850
1095 7550 11/19/2007				
NOVARTIS				
CORPORATE INTELLECTUAL PROPERTY				
ONE HEALTH PLAZA 104/3				
EAST HANOVER, NJ 07936-1080				
EXAMINER				
RAO, DEEPAK R				
ART UNIT		PAPER NUMBER		
1624				
MAIL DATE		DELIVERY MODE		
11/19/2007		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/502,291

Applicant(s)

BORNSEN ET AL.

Examiner

Deepak Rao

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 April 2005.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-41 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 21-29, 31 and 33-41 is/are rejected.
7) ☒ Claim(s) 30 and 32 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/5508)
Paper No(s)/Mail Date 20050617 & 20060929
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Claims 21-41 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating tumor of the brain, does not reasonably provide enablement for a compound or pharmaceutical composition for therapeutic treatment generally; or a method of treating a proliferative disorder generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 35 is drawn to 'a compound for use in a method for the therapeutic

treatment' and claim 37 is drawn to 'a pharmaceutical composition for the treatment of a proliferative disorder'. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claim 40 is drawn to 'a method of treating proliferative disorder', however, it is not recited which proliferative diseases are included in the claim. The claim language covers any and all types of cancers or proliferative diseases. The instant claims cover 'proliferative diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

Test assays and procedures are provided in the specification pages 9-13, to determine activity related to some kinases, however, there is nothing in the disclosure regarding how this test data correlates to the treatment of all types of proliferative disorders encompassed by the instant claims. The instant method includes all types of proliferative disorders including many types of cancers or tumors, some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of the specific treatment is identified and further, how all types of cancers are treated. See MPEP § 2164.03 for

Art Unit: 1624

enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36. This is clearly indicative of the fact that the therapeutic role of these types of inhibitors is very speculative.

The instant claims are drawn to 'a method of treating proliferative disease', which diseases include 'cancer'. No compound has ever been found to treat proliferative diseases or cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). A 'disease caused by proliferation of tumor cell' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus,

such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or proliferative diseases generally.

Further, there is no established single antiproliferative therapeutic agent for all these types of diseases, which are characterized by the proliferation of tumor cells. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states, that "Treatment programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as

Art Unit: 1624

the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating a proliferative disease; a method of detecting or identifying HDAC in a biological sample using the invention compound; and a combination of the invention compound with other anti-cancer agents.

2) The state of the prior art: There are no known compounds of similar structure, which have been demonstrated to treat patients suffering from all types of proliferative diseases including cancer.

3) The predictability or lack thereof in the art: Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases

involving physiological activity such as the instant case, 'the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved'. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in an article (Exp. Opin. Ther. Patents, 1997) stated that "The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one of ordinary skill in the art to use the compounds in the treatment of all of the diseases or disease symptoms within the scope of the claims. The specification provides (see pages 9-13) tests for the measurement of kinase inhibitory activity of the compounds. However, there is no disclosure regarding how this data correlates to treatment of all types of proliferative diseases, including all types of cancer.

6) The breadth of the claims: The instant claims embrace treating all types of proliferative diseases, including all types of cancer.

7) The quantity of experimentation needed would be an undue burden because it is not known what type of 'diseases' are referred to in the claims. Further, it would be an undue burden on one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the medical conditions or illnesses included in the instant claims.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the

unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-26 and 34-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 21, in the definition of A, in the term " $-\text{OR}_3\text{R}_6$ " the oxygen atom is trivalent, i.e., the above term contains an oxygen atom with more attachments than permitted by the available valencies and therefore, the resulting compound will have a charge. The specification does not properly provide explanation of such compounds with appropriate examples.
2. Claim 34 is a substantial duplicate of claim 21. Claim 21 is drawn to 'a compound' which is useful as a pharmaceutical agent and therefore, is expected to be in 'pure form'.
3. Regarding claim 35, the phrase "including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. The discrepancy also appears in 37 and 40.
4. Claims 38 and 39 provide for the use of the compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process

applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

5. In claim 41, the recitation "if so desired" is confusing. It is suggested that the recitation be replaced with more acceptable language, for example, -- optionally --.

Claim Rejections - 35 USC § 101

Claims 38 and 39 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

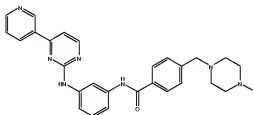
A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21 and 34-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Flynn et al., U.S. Patent No. 7,279,576 (effective filing date December 31, 2002). The instant claims read on reference disclosed compound, see the compound of Example 20 (depicted below for convenience):

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-24, 27-29, 31 and 33-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann, U.S. Patent No. 5,521,184. The reference teaches a generic group of N-phenyl-2-pyrimidine-amine compounds, which embraces applicant's instantly claimed compounds. See formula (I) in col. 1 wherein one of R₄-R₈ is a radical of formula (II) and the remaining may be selected from unsubstituted or substituted lower alkyl, including hydroxyl substituted lower alkyl. The reference teaches that the R₁ substituent may be a pyridine N-oxide or N-oxido-pyridyl. The reference further discloses compounds wherein R₁₀ of formula (II) is phenyl substituted by 4-methylpiperazinyl substituted lower alkyl, see for example, the compound of Example 19 (depicted below for convenience):



The compounds are taught to be useful as pharmaceutical therapeutic agents for tumoral diseases, see the abstract. The instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. For example, the instant claims differ by having a N-oxido-pyridyl in place of pyridyl disclosed for the reference compound. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would

have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocrraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Duplicate Claims

1. Applicant is advised that should claim 21 be found allowable, claims 34 and 35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 34 and 35 do not further limit the compound of claim 21.
2. Applicant is advised that should claim 36 be found allowable, claim 37 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 37 does not further limit the composition of claim 36.

Allowable Subject Matter

Claims 30 and 32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statements filed on June 27, 2005 and September 29, 2006 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

Art Unit: 1624

system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**/Deepak Rao/
Primary Examiner
Art Unit 1624**

November 19, 2007